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(54) Title: USE OF COMPOUNDS AS FUNCTIONAL ANTAGONISTS TO THE CENTRAL CANNABINOID RECEPTORS

(57) Abstract: The invention refers to the use of saturated fatty acid acylamide derivatives as functional antagonists to the central cannabinoid receptors. These molecules, per se devoid of the psychotropic effects of classic cannabinoids, aminoalkylindoles, endocannabinoids known today, have the ability to behave as functional antagonists of the central cannabinoid receptors, when administered by different routes. For their pharmacological activity they are therefore suitable as drugs in pathological states or disorder which can be controlled through a reduction in the functionality of said receptors or through a reduction of the effect of the same endocannabinoids also caused by a reduced availability or affinity of the receptors.

WO 03/006007 A1

USE OF COMPOUNDS AS FUNCTIONAL ANTAGONISTS TO THE CENTRAL CANNABINOID RECEPTORS

FIELD OF THE INVENTION

The present invention is related to the use of acylamides as functional antagonists
5 to the central cannabinoid receptors.

STATE OF THE ART

Cannabis sativa, in addition to being one of the most diffuse recreational drugs in the world, has been used for medical reasons for centuries for its multiple pharmacological effects, the use of which has, however, been limited in the last
10 century mostly for its psychoactive effects on the CNS. The principal active component identified is Δ^9 -tetrahydrocannabinol (Δ^9 -THC) which, in fact, in addition to possessing psychotropic activity, produces an innumerable series of pharmacological effects both in humans and in animals demonstrating therefore great therapeutic potential, however limited by the central effects mentioned.

15 Research into Δ^9 -THC, has, in the last fifteen years, brought about the discovery of the cannabinoid receptors and, more recently, to lipid substances, such as for example anandamide (ANA) and 2-arachidonylglycerol (2-Arach), considered as the natural endogenous ligands for these receptors (*Martin B.R. et al. 1999 Life Sci. 65, 573-595*). These receptors, together with the ligands just described,
20 constitute the said "endocannabinoid system" (*Piomelli D. et al. 2000 TIPS 21, 218-224*).

In the "endocannabinoid system" two receptors have to date been identified: i) the so-called central receptor, because it was initially identified in areas of the CNS and considered the molecular transducer of the central effects of cannabinoids
25 and ii) the so-called peripheral receptor initially identified in peripheral tissues and in turn however considered the molecular transducer of the peripheral effects. The central receptors are present in fact in high concentrations in the CNS, and more precisely in the cerebral cortex, hippocampus, caudate-putamen nuclei, substantia nigra, pars reticulata, globus pallidus, endopeduncular nucleus, cerebellum and
30 spinal medulla. Although to a lesser degree, central receptors are however also present at the peripheral level principally in correspondence with nerve endings as for example in the intestine, as well as on endothelium and on immunocompetent

cells. Instead, peripheral receptors have been principally identified at the peripheral level and above all in immunocompetent cells as for example T-lymphocytes, mastocytes, macrophages, etc. There is no evidence to support their expression in the CNS of adult animals, although their expression has been observed *in vitro* in newborn mouse granular cells and in microglia cells *in vitro* (Skaper S.D. *et al.* 1996 *Proc. Natl.Sci.* 96, 3984-3989; Ameri A. 1999 *Progr. Neurobiol.* 58, 315-348).

As concerns their effects, the central receptors are considered to mediate not just the "undesired effects" of cannabinoids (such as the psychoactive effects, loss of memory and attention-span, loss of motor co-ordination etc.) but also some of their therapeutically "desired effects" (analgesic effect, anti-hyperalgesic, appetite stimulation, ocular hypotension, etc.). The peripheral receptors, like the central receptors present in the immunocompetent cells, have been associated with the more peripheral effects of cannabinoids as for example the anti-inflammatory effect (Ameri A. 1999 *ref. cit.*).

These discoveries together, have given impetus to the development of a vast series of cannabinomimetic molecules, such as the classical cannabinoid agonists (e.g. Δ^8 -THC, Δ^9 -THC etc.) and non-classical cannabinoid and their derivatives (e.g. CP 55940, HU-210 etc.), derived from the endocannabinoids (e.g. metanandamide, etc.), aminoalkylindoles (e.g. Win 55-212) and molecules capable of interfering with the uptake and the inactivation of the endocannabinoids (e.g. AM 404, trifluoromethylketones, etc.), of potential therapeutic interest for which the applications range from the control of pain and inflammation, to the control of nausea and appetite and the reduction of intraocular pressure. Furthermore, synthetic derivatives have also been characterised, e.g. pyrrolic derivatives (e.g. SR141716, SR144528), with antagonistic activity towards cannabinoid receptors, believed to be useful in the control of eating disorders, in memory improvement and motor activity and for the weaning from dependency in tobacco as well as *cannabis* smokers (Ameri A. 1999 *ref. cit.*).

Although it is potentially possible to distinguish the effects mediated by central receptors from those mediated by peripheral receptors, to date, the majority of the cannabinomimetic molecules synthesised do not possess selectivity and receptor

specificity so as to be used without incurring the undesired effects of the cannabinoids. In fact, although they have different receptor binding characteristics, both classical cannabinoids and their derivatives, the aminoalkylindoles and also the endocannabinoids and their derivatives, possess activities both towards central receptors and the peripheral receptors (*Martin B.R. et al. 1999 ref. cit.; Khanolkar A.D. et al. 2000 Chem. Phys. of Lipids 108, 37-52*). To date only a few molecules have been identified possessing a sensitive receptor selectivity and amongst these we find: synthetic pyrazole derivatives to which antagonistic activity specific for central receptors (SR 141716) and for peripheral receptors (SR 144258) has been attributed; CP55940, HU210 etc. with agonistic activity principally towards central receptors and HU-308, JTE-907 and palmitoylethanolamide (PEA) and analogues with agonistic activity towards peripheral receptors. These latter molecules, therefore, not possessing related activity towards central receptors, are devoid of central effects of the cannabinoids and, as such, have been indicated above all as molecules essentially endowed with anti-inflammatory activities, in that they are able to inhibit the pro-inflammatory activation of mastocytes through the specific interaction with the peripheral receptors present on these cells (*WO 9618600 and WO 9618391*). More specifically PEA, togetherwith the endocannabinoid ANA, belongs to the N-acylethanolamides (NAE) class. This family comprises derivatives of ethanolamine conjugated with acid radicals, both saturated (PEA) and unsaturated (ANA). Both ANA and PEA can be produced and released by neuronal cells following excitation suggesting that these molecules may act as neurotransmitter belonging to the endocannabinoids system. However, whilst the acute administration of anandamide *in vivo* provokes cannabinoid-like effects, such as hypothermia, hypomotility, catalepsy, etc., these effects have never been reported after administration of PEA *in vivo*, a result compatible with the absence of affinity of this molecule for the central receptor. Although PEA and ANA are both able to exercise anti-inflammatory effects *in vivo*, there are disagreements regarding the capacity of PEA, in contrast to that of ANA, to interact with the peripheral cannabinoid receptors (*Sugiura T. et al. 2000 J. Biol. Chem. 275, 605-612; Facci L. et al. 1995 Proc. Natl. Sci. USA 92, 3376-3380*). In fact, even though it has been

demonstrated that PEA is capable of significantly reducing the release of pro-inflammatory mediators from stimulated mastocytes *in vitro*, through an action on the peripheral receptors expressed on these cells (*Facci L. et al. 1995 ref. cit.*), more recent experiments conducted on transfected cell lines overexpressing the peripheral receptor have demonstrated that PEA is not able to displace the binding of cannabinoidmimetic molecules to this receptor (*Sugiura T. et al. 2000 ref. cit.*). On the other hand, *in vivo* experiments demonstrate that the anti-inflammatory/antipain activities of PEA is reduced following co-administration of the peripheral receptor antagonist SR144528 (*Calignano A. et al. 2001 Eur. J. Pharm. 419, 191-198*). Furthermore, it has been observed that the simultaneous co-administration of PEA and ANA induces a synergic anti-inflammatory/antipain effect (*WO99/60987*) suggesting that the molecules act through two different systems. In fact, whilst the effect of ANA was antagonised by the central receptor antagonist SR141716, the effect of PEA was sensitive to the effect of the peripheral receptor antagonist (*Calignano A. 2001 ref.cit.*).

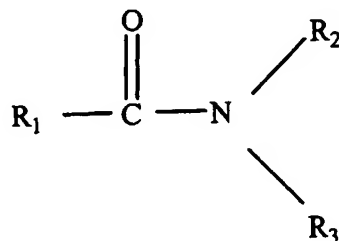
It has to be further pointed out that PEA and analogues have been indicated as possessing neuroprotective activity *in vitro* and as such useful in pathological conditions associated with neuronal death (*WO 9525509 and WO 9618600*). This effect has been observed *in vitro* in newborn mouse cerebellum granule cells which express the peripheral receptor or a CB2-like receptor (*Skaper S.D. et al. 1996 ref.cit.*). Furthermore, a patent application has recently been filed for the use of PEA as a cardio-protective (*WO01/28588*), an effect mediated also in this case likewise by peripheral receptors, because it is antagonised by SR 144528, antagonist of the peripheral receptor, and not by SR 141716, antagonist of the central receptor. It is also noteworthy that the only central effects reported for PEA (antispastic and anticonvulsive), are transitory effects obtained following acute parenteral administration (*Baker D. et al. 2000 Nature 404, 84-87; Lambert D. et al. 2001 Epilepsia 42, 321-327*).

In conclusion, there is no doubt that the evidence available to date indicate that PEA and its analogues are devoid of effects towards the central receptor and that these compounds bring about their effects (anti-inflammatory, painkilling/antipain, neuroprotective, etc.) through the peripheral receptor or however a CB-like

receptor (not CB1 and not CB2) present on immunocompetent cells (e.g. mastocytes) or other cells.

SUMMARY

The applicant has now surprisingly found that following administration the
5 acylamides of saturated acids of general formula (I)



where:

10 $\text{R}_1\text{—CO—}$ can be an acyl residue of a saturated organic acid, linear or branched comprising from 10 to 20 C atoms

—N—R_2 can be:

- an aminohydroxyalkyl residue, linear or branched comprising from 2 to 6 C atoms, optionally substituted with one or more aromatic groups on the alkyl chain

- an aminoacid residue of the series α , β or γ

15 R_3 can be H or CH_3

or where $\text{—N—R}_2, \text{R}_3$ form with the N atom a cyclic aminoether comprising from 5 to 7 C atoms, optionally substituted with linear or branched alkyl groups,

behave as functional antagonists of the central cannabinoid receptors. They can therefore be usefully employed as drugs in pathological states or disorders which
20 can be controlled through a reduction of the functionality of these receptors or through a reduction of the effect of the same endocannabinoids caused by a reduced availability or affinity of the receptors.

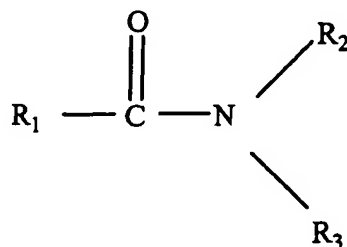
Therefore the subject of the present invention is the use of said saturated acylamides, or esters or salts of the same, for the preparation of pharmaceutical
25 compositions for the treatment of pathological states or disorders connected with an altered functionality and/or "abusive" activation of the central cannabinoid receptors.

DETAILED DESCRIPTION OF THE INVENTION

The aims and advantages of the therapeutic use of the saturated acylamides as functional antagonists of central cannabinoid receptors in pathological states or disorders which can be controlled by reducing the functionality of these receptors or impeding the activity of endocannabinoids, subject of the present invention, will be better understood in the course of the following detailed description.

The applicant has in fact found surprisingly that after repeated administration of saturated acid acylamides, a marked reduction in the receptor density of the central cannabinoid receptors at the level of the spinal medulla, and a reduction of the affinity constant (K_d), still for these receptors, in different cerebral areas (cerebellum, cortex, hippocampus) have been observed. A similar effect is known to occur following a repeated administration of central receptor agonists possessing psychotropic activity, as for example Δ^9 -THC or CP55940 which in fact bring about a variation in receptor density or desensitisation of the central receptor in the areas where this is expressed (*Ameri A.1999 ref. cit.*). No effect however has ever been reported on the central cannabinoid receptors with molecules of the class of the saturated acylamides, as for example PEA, as described in the following.

In the saturated acid acylamides defined by the general formula (I)



where:

R_1-CO- can be an acyl residue of a saturated organic acid, linear or branched, comprising from 10 to 20 C atoms

$-N-R_2$ can be:

- 5 - an aminohydroxyalkyl residue, linear or branched, comprising from 2 to 6 C atoms, optionally substituted with one or more aromatic groups on the alkyl chain, and the hydroxyl group can be optionally esterified with a pharmaceutically suitable acid group, as for example acetic, tartaric and succinic or equivalent
- a residue of an aminoacid of the series α , β or γ in which the carboxylic group
10 can be esterified with pharmaceutically suitable groups, as for example methyl, ethyl, propyl or salified with pharmaceutically suitable counterions as for example sodium, potassium, magnesium or equivalent

R_3 can be H or CH_3

- or where $-N-R_2, R_3$ forms with an atom of N a cyclic aminoether comprising from
15 5 to 7 C atoms optionally substituted with linear or branched alkyl groups,

R_1-CO- can be preferentially selected from the group constituted by aliphatic saturated monocarboxylic acids as for example decanoic acid, lauric, myristic, palmitic, stearic or arachidic acids and

- $-N-R_2$, when present as an aminohydroxyalkyl residue, can be preferentially
20 chosen, for example, from the group constituted by monoethanolamine, 2-hydroxypropylamine, whilst when it is the residue of an α , β or γ aminoacid it can be chosen from the group constituted by serine, glycine, β -alanine, γ -aminobutyric, phenylalanine and tyrosine instead when $-N-R_2, R_3$ form, with an atom of N, a cyclic aminoether, this is preferentially morpholine.

- 25 The saturated acylamides described in the present invention can be prepared according to various methods and preferably through fusion of the alkylamine salt with a carboxylic acid and formation of the corresponding alkylamide, or through acylation of the alkylamine nitrogen with appropriate activated carboxylic derivatives.

- 30 Following are reported, for illustration, and not limiting purpose, some examples of saturated monocarboxylic acid amides.

Example 1: Preparation of N-(2-hydroxyethyl)-palmitoyl amide

100 mmol of ethanolamine, dissolved in 120 ml of dichloromethane was placed in a 250 ml round bottomed flask. To this solution has been added, dropwise, through a loading funnel, 40 mmol of palmitoyl chloride dissolved in anhydrous dichloromethane. The reaction has been maintained with continuous stirring at a
5 temperature of 0-4°C and at the appropriate time, stopped by the addition of a 10% aqueous solution of citric acid. The organic phase has then been anhydrated with anhydrous sodium sulphate and filtered. Using a rotary evaporator at reduced pressure, the solvent has been removed and the solid residue taken up and
10 crystallised with an appropriate solvent.

The yield of the reaction has been approximately 75%.

Physico-chemical properties of N-(2-hydroxyethyl)-palmitoyl amide:

appearance: white crystalline powder

formula: $C_{18}H_{37}NO_2$

15 elemental analysis: C=72.15%; H=12.35; N=4.73; O=10.88

solubility in organic solvents: DMSO, $CHCl_3$, ethanol

solubility in water: insoluble

melting point: 93-95°C

TLC: eluent toluene/ $CHCl_3$, 9/1; R_f =0.42

20 **Example 2: Preparation of N-(3-hydroxypropyl)-palmitoylamide**

80 mmol of 3-amino-1-propanol have been dissolved in 100 ml of dichloromethane in a 250 ml round bottomed reaction flask. To this solution have been added, dropwise, through a loading funnel and with constant stirring, 40 mmol of palmitoyl chloride dissolved in anhydrous dichloromethane. The reaction has been
25 maintained with constant stirring at a temperature of 0-4°C and at the appropriate time, stopped by the addition of a 10% aqueous citric acid solution. The organic phase has then been anhydrated with anhydrous sodium sulphate and filtered. Using a rotary evaporator, at reduced pressure, the solvent has been removed and the solid residue taken up and crystallised with an appropriate solvent.

30 The yield of the reaction has been approximately 88%.

Physico-chemical properties of N-(2-hydroxypropyl)-palmitoyl amide:

appearance: white crystalline powder

formula: $C_{19}H_{39}NO_2$

molecular weight: 313.53

elemental analysis: C=72.51%; H=12.38; N=4.43; O=10.78

solubility in organic solvents: approx. 1 mg/ml in DMSO

5 solubility in water: vary sparingly soluble

melting point: 90-91°C

TLC: eluent $CH_3OH/CHCl_3$ 95/5; R_f =0.38

Example 3: Preparation of N-(3-hydroxypropyl)-lauroylamide

10 In a refrigerated round bottomed flask, have been made to react, for 5 hours at 160°C, 1.73 g of lauric acid (8.65 mmol) and 0.8 g of ethanolamine (13 mmol). The reaction mixture has been then crystallised from 80% ethanol. The crystalline body has been separated by filtration using a buchner, washed three times with cold 80% ethanol and then taken to dryness under vacuum.

The yield of the reaction has been approximately 88%.

15 Physico-chemical properties of N-(2-hydroxyethyl)-lauroylamide:

appearance: white crystalline powder

formula: $C_{14}H_{29}NO_2$

molecular weight: 243.39

elemental analysis: C=68.98%; H=11.95; N=5.73; O=13.35

20 solubility in organic solvents: >10 mg/ml in DMSO

>10 mg/ml in $CHCl_3$

solubility in water: very sparingly soluble

melting point: 86-88°C

TLC: eluent $CHCl_3 - CH_3OH - H_2O - NH_3$, 80/17/2/1; R_f =0.82

25 Example 4: Preparation of N-(2-hydroxyethyl)-stearoylamide

In a refrigerated round bottomed flask, have been made to react, for 5 hours at 160°C, 2.42 g of stearic acid (8.65 mmol) and 0.8 g of ethanolamine (13 mmol).

The reaction mixture has then been crystallised from 95% ethanol. The crystalline body has been then separated by filtration using a buchner, washed three times

30 with cold 95% ethanol and then taken to dryness under vacuum.

The yield of the reaction has been approximately 85%.

Physico-chemical properties of N-(2-hydroxyethyl)-stearoylamide:

appearance: white crystalline powder

formula: $C_{20}H_{41}NO_2$

molecular weight: 243.39

elemental analysis: C=73.18%; H=12.45; N=4.13; O=10.14

5 solubility in organic solvents: approx. 1 mg/ml in $CHCl_3$

solubility in water: insoluble

melting point: 100-101°C

TLC: eluent $CHCl_3$ - CH_3OH - H_2O - NH_3 , 80/17/2/1; R_f =0.82

Example 5: Preparation of N-palmitoyl-morpholinamide

10 In a reaction flask have been dissolved, at 0°C, 0.75 g of morpholine (8.6 mmol) and 0.92 g of triethylamine (9 mmol) in 50 ml of dimethylformamide. To the solution have been added, dropwise, 2.35 g of palmitoyl chloride (8.5 mmol) dissolved in dimethylformamide, and made to react for 1 hour at 0°C and for 5 hours at room temperature. The suspension obtained has been taken to dryness
15 in a evaporator at reduced pressure. The solid residue has then been washed with ethyl ether and crystallised from 70% ethanol. The crystalline body was separated by filtration using a buchner, washed three times with cold 70% ethanol and then taken to dryness under vacuum.

The yield of the reaction has been approximately 90%.

20 Physico-chemical properties of N-palmitoyl-morpholinamide:

appearance: white crystalline powder

formula: $C_{20}H_{39}NO_2$

molecular weight: 325.53

elemental analysis: C=73.52%; H=11.95; N=4.18; O=10.35

25 solubility in organic solvents: >10 mg/ml in DMSO

>10 mg/ml in boiling ethanol

solubility in water: insoluble

melting point: 42-44°C

TLC: eluent $CH_3OH/CHCl_3$ 95/5; R_f =0.90

30 **Example 6: Preparation of N-(2-methoxy-ethyl)-palmitoyl amide**

In a round bottomed reaction flask have been dissolved, at 0°C, 0.75 g of 2-methoxy-ethyl-amine (10 mmol) and 1.1 g of triethylamine (11 mmol) in

tetrahydrofuran. To the solution have been added, dropwise and with constant stirring, 2.75 g of palmitoyl chloride (10 mmol) dissolved in tetrahydrofuran and made to react, for 8 hours at 0°C. To the reaction mixture has been added a double volume of water and the entire mixture extracted three times with ethyl acetate. The combined organic phases, has been washed twice with 1N HCl and a further twice with water. Following anhydration with sodium sulphate, the solvent has been removed in a evaporator under reduced pressure and the residue crystallised from (tert-butyl) methylether and taken to dryness under vacuum.

The yield of the reaction has been approximately 70%.

Physico-chemical properties of N-(2-methoxy-ethyl)-palmitoyl amide:

appearance: white crystalline powder

formula: $C_{19}H_{39}NO_2$

molecular weight: 313.52

elemental analysis: C=72.92%; H=12.22; N=4.69; O=10.17

solubility in organic solvents: >10 mg/ml in ethanol

solubility in water: insoluble

melting point: 75-78°C

TLC: eluent toluene/ethanol/acetic acid 65/30/5; R_f=0.70

Example 7: Preparation of N-lauroyl-morpholinamide

In a round bottomed reaction flask have been dissolved, at 0°C, 0.75 g of morpholine (8.6 mmol) and 0.92 g of triethylamine (9 mmol) in tetrahydrofuran. To the solution have been added, dropwise, 1.86 g of lauroyl chloride (8.5 mmol) dissolved in tetrahydrofuran and made to react, for 1 hour at 0°C and for 5 hours at room temperature. To the reaction mixture has been added an equal volume of water and the entire mixture extracted three times with (tert-butyl) methylether. The combined organic phases, has been washed twice with 1N HCl and a further twice with water. Following anhydration with sodium sulphate, the solvent has been removed in a evaporator under reduced pressure and the residue purified by chromatography on silica gel flushed with hexane/ethyl acetate/acetic acid (79.5/20/0.5). The fractions containing the product have been evaporated in a evaporator under reduced pressure and the residue taken to dryness under vacuum.

The yield of the reaction has been approximately 85%.

Physico-chemical properties of N-lauroyl-morpholinamide:

appearance: white crystalline powder

formula: $C_{16}H_{31}NO_2$

5 molecular weight: 369.43

elemental analysis: C=71.52%; H=11.85; N=5.11; O=11.52

solubility in organic solvents: >10 mg/ml in DMSO

>10 mg/ml in ethanol

solubility in water: insoluble

10 melting point: 20-23°C

TLC: eluent hexane/ethyl acetate/acetic acid, 75/24/1; R_f=0.25

Example 8: Preparation of N-stearoyl-morpholinamide

In a round bottomed reaction flask have been dissolved, at 0°C, 0.75 g of morpholine (8.6 mmol) and 0.92 g of triethylamine (9 mmol) in anhydrous dimethylformamide. To the solution have been added, dropwise, 2.56 g of stearoyl chloride (8.5 mmol) dissolved in anhydrous dimethylformamide and made to react, for 1 hour at 0°C and for 16 hours at room temperature. The reaction mixture has been evaporated under reduced pressure and the residue, after washing with water, has been crystallised first from ethanol and later from tert-butyl-methylether.

20 The crystalline residue has been washed three times with (tert-butyl) methylether and taken to dryness under vacuum.

The yield of the reaction has been approximately 85%.

Physico-chemical properties of N-stearoyl-morpholinamide:

appearance: white crystalline powder

25 formula: $C_{22}H_{43}NO_2$

molecular weight: 325.59

elemental analysis: C=74.12%; H=11.98; N=4.11; O=10.79

solubility in organic solvents: >10 mg/ml in boiling ethanol

solubility in water: insoluble

30 melting point: 58-60°C

TLC: eluent hexane/ethyl acetate/acetic acid, 65/30/5; R_f=0.63

Example 9: Preparation of N-palmitoyl-L-serine

1.02 g of L-serine (10 mmol) have been dissolved at 4°C in 1 M potassium carbonate. To the solution have been added, dropwise and with constant stirring, 2.75 g of palmitoyl chloride (10 mmol). The reaction mixture has been maintained at 0°C for 16 hours and then acidified with 6N HCl. The precipitate has been separated by filtration using a buchner and taken to dryness under vacuum. The residue has been crystallised firstly from (tert-butyl) methylether and later from methanol. The crystalline residue has been washed three times with methanol and taken to dryness under vacuum.

The yield of the reaction has been approximately 80%.

Physico-chemical properties of N-palmitoyl-L-serine:

appearance: white crystalline powder

formula: $C_{19}H_{37}NO_4$

molecular weight: 343.51

elemental analysis: C=66.23%; H=11.08; N=4.19; O=19.50

solubility in organic solvents: >10 mg/ml in DMSO

>10 mg/ml in ethanol

solubility in water: insoluble

melting point: 95-96°C

TLC: eluent chloroform/methanol/water/ammonia, 78/25/2/1; Rf=0.13

Example 10: Preparation of N-lauroyl-L-serine

1.02 g of L-serine (10 mmol) have been dissolved at 4°C in 1 M potassium hydroxide. To the solution have been added, dropwise and with constant stirring 2.20 g of lauroyl chloride (10 mmol). The reaction mixture has been maintained at 0°C for 16 hours and then acidified with 6N HCl and then extracted with ethyl acetate. The organic phase has been anhydrated with sodium sulphate and evaporated in a evaporator under reduced pressure. The residue has been crystallised from acetonitrile. The crystalline residue, separated by filtration, has been washed three times with cold acetonitrile and taken to dryness under vacuum.

The yield of the reaction has been approximately 78%.

Physico-chemical properties of N-lauroyl-L-serine:

appearance: white crystalline powder

formula: $C_{15}H_{29}NO_4$

molecular weight: 287.40

elemental analysis: C=63.02%; H=10.38; N=4.79; O=22.81

5 solubility in organic solvents: >10 mg/ml in DMSO

>10 mg/ml in ethanol

solubility in water: insoluble (soluble >10 mg/ml as sodium salt)

melting point: 121°C

TLC: eluent toluene/ethanol/acetic acid, 65/30/5; R_f =0.50

10 **Example 11: Preparation of N-lauroyl-L-glycine**

1.2 g of glycine (16 mmol) have been dissolved at 4°C in 1 M potassium hydroxide. To the solution have been added, dropwise and with constant stirring, 2.20 g of lauroyl chloride (10 mmol). The reaction mixture has been maintained at 0°C for 16 hours and, following this time, acidified with 6 N HCl and then extracted
15 with ethyl acetate. The organic phase has been anhydrated with sodium sulphate and evaporated in a evaporator under reduced pressure. The residue has been crystallised from acetonitrile. The crystalline residue, separated by filtration using a buchner, has been washed three times with cold acetonitrile and taken to dryness under vacuum.

20 The reaction yield has been approximately 80%.

Physico-chemical properties of N-lauroyl-glycine:

appearance: white crystalline powder

formula: $C_{14}H_{27}NO_3$

molecular weight: 257.37

25 elemental analysis: C=65.02%; H=10.78; N=5.89; O=18.31

solubility in organic solvents: >10 mg/ml in DMSO

>10 mg/ml in ethanol

solubility in water: insoluble (soluble >10 mg/ml at pH 7.5)

melting point: 120°C

30 TLC: eluent toluene/ethanol/acetic acid, 65/30/5; R_f =0.60

Example 12: Preparation of N-palmitoyl-L-glycine

1.2 g of glycine (16 mmol) have been dissolved at 4°C in 1 M potassium

hydroxide. To the solution have been added, dropwise and with constant stirring, 2.75 g of palmitoyl chloride (10 mmol). The reaction mixture has been maintained at 0°C for 16 hours and, following this time, acidified with 6 N HCl and then extracted with ethyl acetate. The organic phase has been anhydrated with sodium sulphate and evaporated in a evaporator under reduced pressure. The residue has been crystallised from ethanol. The crystalline residue, separated by filtration using a buchner, has been washed three times with cold ethanol and taken to dryness under vacuum.

The yield of the reaction has been approximately 70%.

Physico-chemical properties of N-palmitoyl-glycine:

appearance: white crystalline powder

formula: $C_{18}H_{35}NO_3$

molecular weight: 313.48

elemental analysis: C=69.12%; H=11.01; N=4.86; O=15.01

solubility in organic solvents: >10 mg/ml in DMSO

solubility in water: very sparingly soluble

melting point: 120°C

TLC: eluent chloroform/methanol/water/ammonia, 77/25/2/1; Rf=0.15

Example 13: Preparation of N-palmitoyl-β-alanine

1.5 g of β-alanine (17 mmol) have been dissolved at 4°C in 1 M potassium hydroxide. To the solution have been added, dropwise and with continuous stirring, 2.75 g of palmitoyl chloride (10 mmol). The reaction mixture has been maintained at 0°C for 16 hours and, following this time, acidified with 6N HCl and extracted with ethyl acetate. The organic phase has been anhydrated with sodium sulphate and evaporated in a evaporator under reduced pressure. The residue was crystallised from (tert-butyl) methylether. The crystalline residue, separated by filtration using a buchner, has been washed three times with cold (tert-butyl) methylether and taken to dryness under vacuum.

The yield of the reaction has been approximately 85%.

Physico-chemical properties of N-palmitoyl-β-alanine:

appearance: white crystalline powder

formula: $C_{19}H_{37}NO_3$

molecular weight: 327.51

elemental analysis: C=70.11%; H=11.72; N=4.68; O=14.49

solubility in organic solvents: >5 mg/ml in DMSO

>5 mg/ml in ethanol

5 solubility in water: very sparingly soluble

melting point: 122°C

TLC: eluent toluene/ethanol/acetic acid, 65/30/5; R_f=0.60

Example 14: Preparation of N-palmitoyl-γ-aminobutyrate

2.0 g of γ-aminobutyric acid (19 mmol) have been dissolved at 4°C in 1 M
10 potassium hydroxide. To the solution have been added, dropwise and with
constant stirring, 2.75 g of palmitoyl chloride (10 mmol). The reaction mixture has
been maintained at 0°C for 16 hours and, after this time, acidified with 6 N HCl and
then extracted with ethyl acetate. The organic phase has been anhydrous with
sodium sulphate and evaporated in a evaporator under reduced pressure. The
15 residue has been crystallised from (tert-butyl) methylether. The crystalline residue,
separated by filtration using a buchner, has been washed three times with cold
(tert-butyl) methylether and taken to dryness under vacuum.

The yield of the reaction has been approximately 80%.

Physico-chemical properties of N-palmitoyl-γ-aminobutyrate:

20 appearance: white crystalline powder

formula: C₂₀H₃₉NO₃

molecular weight: 341.54

elemental analysis: C=69.81%; H=11.02; N=4.85; O=14.32

solubility in organic solvents: >5 mg/ml in DMSO

25 >5 mg/ml in ethanol

solubility in water: very sparingly soluble

melting point: 102°C

TLC: eluent toluene/ethanol/acetic acid, 65/30/5; R_f=0.70.

The saturated fatty acid amide derivatives herein described, as briefly previously
30 mentioned, have surprisingly been demonstrated to act, after repeated
administration in normal adult rats, as functional antagonists of the central
cannabinoid receptors, in that a reduction of the number of receptors or of their

affinity, results in a reduction of their activity, without determining the cannabinomimetic effects known to be modulated by the central receptors (e.g. hypothermia, motor deficiency, etc.). Moreover, unlike cannabinoids, the derivatives described in the present invention decrease food intake both after acute or chronic administration. The effects on the drastic reduction of the number of the central receptors at the level of the spinal medulla and the significant diminution of the affinity of this receptor in other areas of the CNS are described below in detail. Also described below is the behavioural/pharmacological effect on food intake and body weight after administration of compounds of the present invention.

A) Characterisation of the central cannabinoid receptors in different areas of the CNS

The cannabinoid receptors have been characterised using receptor binding techniques. These analyses have been carried out on cells membrane preparations from different areas of the CNS from animals treated repeatedly with the compounds described herein and compared with animals treated with just carrier.

a) Treatment of animals

Adult male Sprague Dawley rats have been used, weighing 200-300 g (Harlan-Italy, San Pietro al Natisone, UD, Italia). The animals, maintained on "normal" diets, have received two daily administrations (10mg/Kg *per os*) of the compounds herein described, for 10 days.

b) Preparation of rat, nervous tissue-enriched membranes, for central cannabinoid receptor analysis.

The nervous tissue membranes, have been prepared by the removal and rapid freezing at -80°C of the following cerebral areas: spinal medulla, cortex, hippocampus and cerebellum. The tissue, have been weighed and suspended in 30 volumes of cold 50 mM Tris-HCl pH 7.4 buffer containing 0.25% of Soybean Type II Trypsin inhibitor, 1 mM EDTA and 4mM MgCl₂, and has been homogenised with 10 "strokes" in a Potter Teflon/glass homogeniser. After successive centrifugation and washing of the membranes, the pellet has been resuspended in a small volume (approx 1.5ml per g of starting tissue wet weight)

of 50 mM Tris-HCl pH 7.4 buffer containing 1 mM EDTA, 4mM MgCl₂ and 0.05% Fatty Acid Free BSA. Protein concentration has been determined on these samples by the bicinchinonic acid method.

5 c) **Determination of the K_d and B_{max} of the central receptor.** The binding to the central cannabinoid receptors has been carried out in polystyrene tubes in the presence of PMSF, as a protease inhibitor, and DMSO, using ³H-WIN55,212-2 as a labelled ligand, known to bind to cannabinoid receptors. After addition of the membranes, prepared as described previously, the tubes have been incubated for 1 hour at 30°C. The ³H-WIN55,212-2, possessing a high affinity for the central
10 cannabinoid receptors, has been used at a concentration of around 1-2 nM, whilst the final concentration of cold WIN55,212-2 used to obtain the total displacement of the label from its receptors was from 1 to 10µM. For a typical binding experiment, the final volume was 1ml, constituted by: 870 µl of binding buffer, 10 µl of DMSO, 10 µl of ³H-WIN55,212-2 100nM, 10 µl of PMSF 1mM in 1% DMSO
15 and 100 µl of synaptosomal membrane enriched preparation from nervous tissue (concentration of the homogenate around 1-2 µg of protein per µl). At the end of the incubation period the samples have been filtered through Whatman GF/C filters using a *cell harvester*. The filters have then been washed with buffer (3X5 ml) and dried in a warm-air drier. Once dried they have been inserted into vials
20 containing three millilitres of scintillation liquid and the radioactivity measured with a liquid scintillation Beta Counter. The values obtained from samples used to measure non-specific binding have been subtracted from these for total binding, thus obtaining the values for specific binding.

The results obtained with respect to the K_D and B_{max} of the central receptor with
25 the compounds described are reported in table 1.

TABLE 1

TISSUE	TREATMENT	K_D (nM)	B_{max} (pmol/mg prot)
Medulla	Control	2.8 ± 0.8	817 ± 83
	Example 1	1.3 ± 0.4	220 ± 17
	Example 4	1.6 ± 0.6	480 ± 95
Cortex	Control	1.6 ± 0.2	1880 ± 67
	Example 1	2.2 ± 0.5	1840 ± 92
	Example 4	2.0 ± 0.4	1825 ± 85
Hippocampus	Control	1.5 ± 0.3	640 ± 26
	Example 1	2.4 ± 0.3	676 ± 26
	Example 4	2.1 ± 0.5	652 ± 28
Cerebellum	Control	1.9 ± 0.5	1325 ± 98
	Example 1	4.5 ± 1.2	1315 ± 102
	Example 4	2.8 ± 0.7	1338 ± 112
	Example 5	3.0 ± 0.8	1356 ± 93

The results obtained, *in vivo*, demonstrate that the repeated administration of saturated acid amide derivatives are able to reduce the affinity, for WIN 212,55-2, of the central cannabinoid receptors in the cerebellum, hippocampus, cortex, without changing the number of receptors (B_{max}). It should be remembered that there is no experimental evidence for the presence of peripheral cannabinoid receptors in the CNS of adult rats. In the medulla, where it is known that only central cannabinoid receptors are present, one can see an increase in affinity for WIN 212,55-2 by these receptors. Regarding this it is noted that the increase in affinity of the central cannabinoid receptors corresponds with an evident reduction of the number of receptors expressed. This increase in receptor affinity is probably the result of an adjustment of the system induced by the strong reduction in the number of receptors, by about 75%, induced by the repeated administration of saturated acid amidic derivatives. In any case, the strong reduction in the number of central receptors seen at the medullar level, and the reduction of the affinity of

the central receptor in the cerebellum, hippocampus and in the cortex, show that these molecules act as functional antagonists of the central cannabinoid receptors.

B) In vivo effect on food intake and body weight

a) Animals and Treatments

- 5 Balb/c mice (18-22 g) were housed single per cage under standard conditions. Drugs were dissolved in a vehicle consisting of cremophor/ethanol/saline (1:1:18 by volume) or suspended in carboxymethylcellulose (CMC) 0.5% in PBS.

b) Feeding experiments

- 10 All the experiments were performed in the morning (between 10.00 and 13.00) in a soundproof, air-conditioned room.

For acute experiments, food intake was measured in mice deprived of food for 18 h. Drugs or vehicle were administered 60min before food presentation. Food intake was measured as difference between food pellet weight before and after 1h (table 2 and 3).

- 15 In sub-chronic experiments, body weight of freely fed mice was recorded every day before receiving, per os, a subsequent administration of vehicle or drug for a total of four days (table 4).

c) Statistical evaluation

- 20 Results are presented as means \pm SEM and were analysed with an analysis of variance ANOVA followed by Student-Newman-Keuls' test with the level of significance set at $P=0.05$.

Table 2. Food intake, in 18 hrs starved mice, 1 hour after "per os" administration of a single dose of SEA.

<i>Treatment</i>	<i>Food intake (g)</i>	<i>S.D.</i>	<i>% of control</i>	<i>S.D.</i>
Control	0,371	0,057	100	15,34
SEA (ex. 4) 5 mg/kg (os)	0,223	0,050	60,13	13,71
SEA (ex. 4) 10 mg/kg (os)	0,186	0,062	50,02	16,69
SEA (ex. 4) 25 mg/kg (os)	0,171	0,045	46,01	12,16
Stearcic Ac + Ehanolamine 25 mg/kg (os)	0,335	0,041	90,26	11,23

- 25 Table 3. Food intake, in 18 hrs starved mice, 1 hour after subcutaneous or intraperitoneal administration of a single dose of PEA .

<i>Treatment</i>	<i>Food intake (g)</i>	<i>S.D.</i>	<i>% of control</i>	<i>S.D.</i>
<i>Control</i>	0,79	0,063	100	12,1
<i>PEA (ex. 1) 10 mg/kg (sc)</i>	0,57	0,048	73,08	11,2
<i>PEA (ex. 1) 10 mg/kg (ip)</i>	0,49	0,045	62,03	13,7

Table 4. Percent of body weight loss in sub-chronic treatment with SEA.

<i>Treatment</i>	<i>Percent of body weight loss</i>			
	<i>T=0</i>	<i>T=1</i>	<i>T=2</i>	<i>T=3</i>
<i>Control</i>	-8,7	-4,5	-0,6	1,3
<i>Sea (ex. 4) 5mg/kg</i>	-9,3	-5,0	-0,1	1,9
<i>Sea (ex. 4) 10mg/kg</i>	-9,0	-9,5	-4,7	-1,2
<i>Sea (ex. 4) 25mg/kg</i>	-9,7	-8,9	-8,1	-8,2
<i>Stearic Acid+Ethanolamine</i>	-9,1	-4,6	-2,8	-2,8

The present invention describes therefore an effect on the central cannabinoid receptors following single or repeated administrations of saturated acid N-acylamides characterisable as a functional antagonistic type effect towards these receptors. These compounds are therefore suitable for use, alone or in association with other compounds, in the treatment of symptomatology, associated with different disorders and pathological states, controllable through a reduction of activity and/or functionality of the central cannabinoid receptors.

a) the involvement of the central cannabinoid receptors in the loss of control, both pyramidal and extrapyramidal, of movement and of motor activities, in ataxia and in hypoesthesia (*Ameri A. 1999 ref.cit.; Patel S. and Hillard C.J. 2001 J. Pharmacol.Exp. Ther. 297, 629-637*);

b) the involvement of the central cannabinoid receptors in loss of memory, learning and attention capability (*Ameri A. 1999 ref.cit.*);

c) the recent demonstration of a possible role of the endocannabinoid system in psychic function and in schizophrenia (*Piomelli D. et al. 2000 ref. cit.; Ameri A. 1999 ref.cit.*);

d) that it has been recently demonstrated that chronic treatment with classical cannabinoids, known to be associated with the reduction of receptor density or with the desensitisation of the central cannabinoid receptors, results in a reduction

in opiod tolerance (*Ameri A. 1999 ref.cit.*);

e) the capability of the antagonists of the central cannabinoid receptors to lower the pharmacological dependence on drugs and/or abuse substances, such as opiods, alcohol, marijuana, amphetamines and tobacco (*Huestis M.A. et al. 2001 Arch. Gen. Psychiatry 58, 322-328; Mas-Nieto M. et al. 2001 Brit. J. Pharmacol. 132, 1809-1816*);

f) the role of the central cannabinoid receptors in the control of appetite and hunger and the recent indication of the use of the central cannabinoid receptor agonist (SR 141716) as anorexants (*Di Marzo V. et al. 2001 Nature 410, 822-825; Kirkham T.C. and Williams C.M. 2001 Psycopharmacol. 153, 267-270*);

g) the presence of central cannabinoid receptors constitutively expressed in peripheral organs and tissues as for example in the digestive system and the immune system and in the vascular system where cannabinoids agonists have been shown to exert vasodilatative and hypotensive effects (*Izzo A.A. et al. 2000 Brit. J. Pharmacol. 129 984-990; Salzet M. et al. 2000 Eur. J. Biochem 267, 4917-4927; Hillard C. J. 2000 J. Pharmacol. Exp. Therap. 294, 27-32*);

h) the role of central cannabinoid receptors in hypotension induced by endotoxins in advanced stages of liver cirrhosis and the ability of the central cannabinoid antagonists (SR 141716) to induce a vasopressive effect associated with a reduction of the mesenteric arterial flow and of portal venous pressure (*Baktai S. et al. 2001 Nature Med. 7, 827-832*).

From the considerations mentioned above it is however clear that the effect of the acylamides obtained following systemic administration *in vivo* described in the present invention, characterise these compounds as functional antagonists of the central cannabinoid receptors usefully employable therefore for the preparation of pharmaceutical compositions for the therapeutic treatment, alone or in association with other therapeutic agents selected for the specific pathological state or disorders, as for example drugs: anti-epileptics, neuroleptics, atypical neuroleptics, anti-depressives, dopaminergics, dopamine agonists, gaba agonists, weight control drugs, for memory improvement, anti-inflammatory/anti-pain (e.g.. opiods, salicilates, pyrazoles, indoles, arylanthranyles, arylpropionates, arylacetates, oxicam, pyrano carboxylates, glucocorticoids), cathartics (emollients, osmotics,

salines, irritants), of pathologic states or disorder connected with altered functionality and/or "abusive" activation of the central cannabinoid receptors and as such in:

- in the control of motor discoordination as for example those induced by pyramidal and extrapyramidal deficit;
- in the disorders of sensory nerve conduction of hypoesthetic type;
- in neurological disorders characterised by loss of mnemonic, learning and attention capabilities;
- in the therapy of psychotic states as for example schizophrenia and mood and emotional disorders;
- in the reduction of opiod tolerance in antalgic therapy;
- in the weaning from dependency from substances of abuse (e.g. opioids, alcohol, marijuana, amphetamines and tobacco);
- in eating disorders for the control of the stimulation of hunger and of appetite;
- in pathological states of immunodepression, also drug induced, in which an immunostimulant action is necessary;
- in the control of intestinal motility and of blood pressure also in states of advanced cirrhosis.

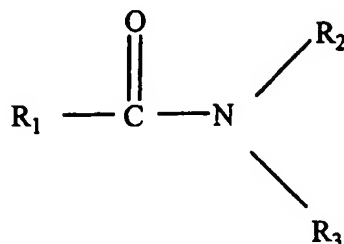
The administration routes that can be used for the preventive or therapeutic treatment of the pathological states or disorders according to the present invention can be oral, parenteral, intramuscularly, subcutaneous or intravenously, and the topical administrations can be transdermical, including rectal, sublingual and intranasal. The compounds, according to the therapeutic use as functional antagonists of the central cannabinoid receptors, can be administered in pharmaceutical compositions in combination with excipients, dispersants and diluents compatible with the pharmaceutical uses known or new, with the aim of obtaining an improved delivery of the active ingredient to the site of action and to obtain a rapid effect, sustained or delayed in time. For this aim therefore fast, sustained or slow release pharmaceutical compositions can be used. The dosages are dependent on the severity of the pathology or disorder and on the chosen route of administration, as well as on the state (age, body weight, general health condition) of the patient. For illustrative purposes, but not limiting the preset

invention, the dosage may range between 1 mg/Kg and 50 mg/Kg in daily repeated administrations for a period ranging from 2 to 16 weeks.

For oral administration, compositions in the form of dispersible granular powders, tablets, pills, hard and soft gelatine capsules, suspensions are suitable; for
5 parenteral administration intramuscularly, subcutaneously, intravenously or peridurally, compositions in the form of buffered aqueous solutions, oil suspensions or lyophilised powders dispersible in appropriate solvents at the time of administration can be suitable; for topical administration transdermally, rectally, intranasally or sublingually, compositions in appropriate excipients or dispersants
10 in the form of patches, suppositories, ovules, aerosols and sprays can be suitable.

Claims

1. Use of a saturated acid acylamide of formula (I)



or esters or pharmaceutically acceptable salts of the same, where:

$\text{R}_1\text{--CO--}$ is an acyl residue of a saturated organic acid, linear or branched comprising from 10 to 20 C atoms,

10 --N--R_2 is:

- a residue of a linear or branched aminohydroxyalkyl comprising from 2 to 6 C atoms, optionally substituted by one or more aromatic groups on the alkyl chain,
- an aminoacid residue of the series α , β or γ ,

R_3 can be H or CH_3

15 or where

$\text{--N--R}_2, \text{R}_3$ form with the N atom a cyclic aminoether comprising from 5 to 7 C atoms, optionally substituted with linear or branched alkyl groups,

as functional antagonists of central cannabinoid receptors for the preparation of pharmaceutical compositions for the preventive or therapeutic treatment of pathological states or disorders associated with altered functionality and/or "abusive" activation of central cannabinoid receptors;

20 2. The use according to claim 1 characterised by the fact that the acyl residue $\text{R}_1\text{--CO--}$ is chosen from the group constituted by aliphatic, saturated, monocarboxylic acids;

25 3. The use according to claim 2 where the acyl residue is chosen from the group constituted by decanoic, lauryl, myristic, palmitoyl, stearic or arachidic acid;

4. The use according to claim 1 characterised by the fact that, when --N--R_2 is a

linear or branched aminohydroxyalkyl residue, this is chosen from the group constituted by monoethanolamine or 2 hydroxypropylamine;

- 5 5. The use according to claims 1 and 4 characterised by the fact that the hydroxyl of the aminohydroxyalkyl residue is esterified with a pharmaceutically suitable acid group;
6. The use according to claim 1 characterised by the fact that, when $-N-R_2$ is an aminoacid residue of the series α , β or γ , this is chosen from the group constituted by serine, glycine, β -alanine, γ -aminobutyric, phenylalanine or tyrosine;
- 10 7. The use according to claims 1 and 6 characterised by the fact that the carboxylic group of the aminoacid residue is esterified with groups or salified pharmaceutically suitable counterions;
8. The use according to claim 1 characterised by the fact that, when $-N-R_2, R_3$ form with the N atom a cyclic aminoether, this is morpholine;
- 15 9. The use according to claim 1 characterised by the fact that said pathological states are chosen from the group constituted by motor activity disorders derived from pyramidal and extrapyramidal;
10. The use according to claim 1 characterised by the fact that said pathological states are chosen from the group constituted by disorders of sensory nerves of hypoesthetic type;
- 20 11. The use according to claim 1 characterised by the fact that said pathological states are chosen from the group constituted by neurological disorders characterised by losses in mnemonic, learning and attention capability;
12. The use according to claim 1 characterised by the fact that said pathological states are chosen from the group constituted by psychotic states and humour and emotional disorders;
- 25 13. The use according to claim 1 characterised by the fact that said disorders are opiod tolerance in antalgic therapy;
14. The use according to claim 1 characterised by the fact that said disorders are associated with the withdrawal syndrome of substances of abuse in the weaning of the same.
- 30 15. The use according to claim 1 characterised by the fact that said disorders are

eating disorders or habits;

16. The use according to claim 1 characterised by the fact that said disorders are chosen from the group in which an immunostimulant action is required;

5 17. The use according to claim 1 characterised by the fact that said disorders are chosen from the group constituted by disturbances in intestinal motility;

18. The use according to claim 1 characterised by the fact that said pathological states are chosen from the group constituted by blood pressure disturbances including advanced states of liver cirrhosis;

10 19. The use according to claims 9 to 18 characterised by the fact that in said pathological states the therapeutic compositions containing acylamides of saturated acids, or esters or salts of the same, can be used alone or in association with medications chosen for the same;

15 20. The use according to claim 1 characterised by the fact that said pharmaceutical compositions are suitable for oral administration in the form of dispersible granular powders, tablets, pills, soft or hard gelatine capsules, suspensions;

21. The use according to claim 1 characterised by the fact that said pharmaceutical compositions are suitable for administration, parenterally intramuscularly, subcutaneously, endovenously or peridurally, in the form of buffered aqueous solutions, oil suspensions or lyophilised powders dispersible in appropriate
20 solvents at the time of administration;

22. The use according to claim 1 characterised by the fact that said pharmaceutical compositions are suitable for administration, topically transdermally, rectally, intranasally or sublingually, in appropriate excipients or dispersants in the form of patches, suppositories, ovules, aerosols and sprays.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/07722

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/195 A61P1/00 A61P25/30 A61P37/00 A61P1/16
A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, PAJ, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 18600 A (LIFEGROUP SPA ;DELLA VALLE FRANCESCO (IT); LEON ALBERTA (IT); MARC) 20 June 1996 (1996-06-20) page 50; examples 1,2,7,8,10,11 ---	1-10,16, 19-22
X	US 5 990 170 A (DELLA VALLE FRANCESCO ET AL) 23 November 1999 (1999-11-23) column 4 column 37; examples 12,14,23,24,29,35-37 ---	1-10,16, 19-22
A	SALZET MICHEL ET AL.: "Comparative biology of the endocannabinoid system" EUR. J. BIOCHEM., vol. 267, 2000, pages 4917-4927, XP001120429 the whole document --- -/--	1-10,16, 19-22



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

International Application No

PCI/EP 02/07722

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VAMVAKIDES A: "CATALEPSIE CHEZ LE RAT APRES HALOPERIDOL ET QUELQUES NOUVEAUX GABA-ERGQUES" AGRESSOLOGIE, XX, XX, vol. 25, no. 9, 3 December 1983 (1983-12-03), pages 1011-1016, XP002064200 page 1015 ---	1-12, 19-22
X	US 5 925 678 A (DELLA VALLE FRANCESCO ET AL) 20 July 1999 (1999-07-20) column 6 column 12 column 15 ---	1-12, 19-22
A	PUOMELLI, DANIEL ET AL.: "The endocannabinoid system as a target for therapeutic drugs" TIPS, vol. 22, 2000, pages 218-224, XP002222935 page 222 -page 223 ---	1-12, 19-22
A	MAS-NIETO, MAGDALENA ET AL.: "Reduction of opiod dependence by the CB1 antagonist SR141716A in mice: evaluation of the interest in pharmacotherapy of opiod addiction" BRIT. J. PHARMACOL., vol. 132, 2001, pages 1809-1816, XP009001232 the whole document ---	1-10,13, 14,19-22
Y	IZZO A A ET AL: "MODULATION OF PERISTALSIS BY CANNABINOID CB1 LIGANDS IN THE ISOLATED GUINEA-PIG ILEUM" BRITISH JOURNAL OF PHARMACOLOGY, BASINGSTOKE, HANTS, GB, vol. 129, no. 5, March 2000 (2000-03), pages 984-990, XP000997205 ISSN: 0007-1188 page 990 ---	1-10,17, 19-22
P,Y	CAPASSO R ET AL: "Inhibitory effect of palmitoylethanolamide on gastrointestinal motility in mice." BRITISH JOURNAL OF PHARMACOLOGY. ENGLAND NOV 2001, vol. 134, no. 5, November 2001 (2001-11), pages 945-950, XP001120406 ISSN: 0007-1188 page 945 page 948 --- -/--	1-10,17, 19-22

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/07722

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>BÁTKAI S ET AL: "Endocannabinoids acting at vascular CB1 receptors mediate the vasodilated state in advanced liver cirrhosis." NATURE MEDICINE. UNITED STATES JUL 2001, vol. 7, no. 7, July 2001 (2001-07), pages 827-832, XP001120431 ISSN: 1078-8956 the whole document</p> <p>---</p>	1-10, 18-22
A	<p>AMERI A: "The effects of cannabinoids on the brain." PROGRESS IN NEUROBIOLOGY. ENGLAND JUL 1999, vol. 58, no. 4, July 1999 (1999-07), pages 315-348, XP001120318 ISSN: 0301-0082 the whole document</p> <p>---</p>	1-22
A	<p>MARTIN B R ET AL: "Discovery and characterization of endogenous cannabinoids." LIFE SCIENCES. ENGLAND 1999, vol. 65, no. 6-7, 1999, pages 573-595, XP001120432 ISSN: 0024-3205 the whole document</p> <p>---</p>	1-22
T	<p>RICE A S C: "CANNABINOIDS IN PAIN" CURRENT OPINION IN INVESTIGATIONAL DRUGS, CURRENT DRUGS, LONDON, GB, vol. 2, no. 3, March 2001 (2001-03), pages 399-414, XP001119594 ISSN: 0967-8298 the whole document</p> <p>-----</p>	1-22

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-22 relate to a large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds described in examples 1-14.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/07722

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/07722

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9618600	A	20-06-1996	IT MI942513 A1	14-06-1996
			AT 184591 T	15-10-1999
			AU 4344196 A	03-07-1996
			CA 2207804 A1	20-06-1996
			DE 69512273 D1	21-10-1999
			DE 69512273 T2	11-05-2000
			WO 9618600 A1	20-06-1996
			EP 0799188 A2	08-10-1997
			JP 11501615 T	09-02-1999
US 5990170	A	23-11-1999	IT MI942512 A1	14-06-1996
			AU 4344296 A	03-07-1996
			EP 0799033 A1	08-10-1997
			JP 11500411 T	12-01-1999
			CA 2207850 A1	20-06-1996
			WO 9618391 A2	20-06-1996
US 5925678	A	20-07-1999	IT 1271623 B	04-06-1997
			AU 2109095 A	09-10-1995
			DE 69510825 D1	19-08-1999
			EP 0804179 A2	05-11-1997
			JP 9510467 T	21-10-1997
			AT 182075 T	15-07-1999
			CA 2186243 A1	28-09-1995
			WO 9525509 A2	28-09-1995